REMARKS

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Right now is a particularly awkward time to frame any useful commentary on developmental biology. The field has had enough fancy; more recently its methodology has been under enormous pressure to accommodate the inspirations of molecular biology and the models of development that can be read into microbial genetic systems. But now, as this volume amply shows, it is responding.

Why did the editors invite me into this "tender trap" to begin with? The main excuse may have been an unguarded remark I once made that "embryology should be studied with embryos." Since, at the time, most of my colleagues, and I myself, were professing to be studying embryology better than the embryologists could, by applying ourselves to regulation and quasi-heredity in microbes, e.g., antigenic variation in *Salmonella,* this profession may have endeared me to the guild. A less endearing remark I made a few years later that "embryology was about to begin" may have been the final goad to the editors to make sure that I would read this book, and see that it indeed had begun. For that at least, I am duly grateful. I hope that my colleagues in molecular biology will read this volume, and the ones to follow, especially as more and more of them become impatient to furnish the one missing concept or technique that will illuminate the whole problem of development, once and for all.

If I have any criticism to offer of the organization of the pioneering volume of this serial publication, it would be just against the spirit of my earlier remark about embryos—namely, that the "developmental" analysis of bacteriophage is so cogent that its omission is inexcusable—even if it were beyond the persuasive capabilities of the editors to collect a pledge. (Dr. Sussman quotes some of the texts in his article.)

Despite the mechanistic flavor of the now classic work on tissue induction, embryology has historically had more than its share of mysti-

cism, with some mysterious property of "organization" always in the background to inhibit bold experiments. There is relatively little of that now, but the working hypothesis should be brought out into the open. The point of faith is: make the polypeptide sequences at the right time and in the right amounts, and the organization will take care of itself. This is not far from suggesting that a cell will crystallize itself out of the soup when the right components are present. And it might be worth thinking of experiments capable of such a result at that! This faith has no foundation except a modicum of empirical success in accounting for a problem that most of us would have thought to be the ultimate bastion of jealous Nature's secrecy, the biochemistry of gene replication. True, "organizational" factors doubtless play a large role in the integrity of the hereditary process. But now is the time to study them, when they are a challenge to explicit experimentation, rather than a lid over a porthole. For the most part, organization seems to be turning out to be quite comprehensible, even to the unaided human mind, as one more level of macromolecular chemistry.

Should we be hopeful that developmental biology will be cleaned up in one more decade? It probably could be done, in an orderly way, but not before there is a concensus both about the nature of the problem (which can perhaps be found) and especially the choice of experimental material. The central problem is twofold: (1) How is the time-ordered sequential program of protein synthesis generated from the cell's *informaton,* and (2) What is the character of epinucleic heredity, i.e., the restrictive information transmitted in tissue lines that cannot sensibly be attributed to DNA-sequence codes. In thinking about (1) one can hardly help but be profoundly influenced by the Jacob–Monod operon[1] models, which had their roots in part in studies, like those of Barbara McClintock, on inhibition of proximate genes in a chromosome field. But the authors of these models would be the first to decry a slavish adherence to their detailed manifestation as seen in bacteria. Even at a cytological level, as we now know, bacterial chromosomes are importantly simpler in structure than the metazoan. As soon as some concrete facts were brought out it was as foolish to persist in the analogy as it would have been to ignore it in the early attack on bacterial genetics. The logical design of metazoan chromosomes is quite different too. Coordinate regulation of genes in a biosynthetic sequence in bacteria is almost always correlated by

[1] Beautifully reviewed in Jacob's Nobel Prize lecture (*Science* 152:1470-1478, 1966).

close linkage of these genes, i.e., to form an operon. As against dozens of examples in bacteria, it is not clear whether there are any in metazoa. Note, for example, the *non*-linkage of the hemoglobin-α and -β factors; and certainly as no mere coincidence or vestige of duplication, β and γ are linked, and these are competitive, not coordinated, in synthesis. Even more spectacular, each of the genes for a recognizable step in the biosynthesis of the ABO blood group system, *I, Le, Se, H,* is dispersed in the chromosome set. If the corresponding enzymes are coordinated, it must be by some quite different mechanism, not coordination within an operon. The Rh complex might be cited as a counter-example, if *C, D, E* are regarded as linked genes. However, the position effect leading to qualitatively distinguishable products from this system hints that these components concern different segments of a single molecule, i.e., that the Rh complex is a single cistron, not an operon containing a series of cistrons. Many other blood group factors, of uncertain but possible affinity to the ABO mucopolysaccharide, are also dispersed. We should then be searching for some other correspondence principle, evolved as an alternative to the operon, whereby genes on different chromosomes can still be coordinated. The work to prove may be harder than the wit needed to think of a number of possibilities.

The variability in total DNA content of the nucleus among plant or animal species of similar complexity points to the triviality of function of large parts of it. Organisms that have a generation time larger than thirty minutes can afford to be extravagant with DNA synthesis. G. L. Stebbins[2] has suggested that the excess DNA is analogous to the inter-record gaps on a computer tape—which can sometimes be used to regulate the pace of a tape-controlled process. To turn a computer into a clock may be an extravagance, but it is sometimes cheaper than designing a new piece of hardware. At any rate, this is one way of rescuing human self-esteem from derogation by a salamander's thirtyfold excess of DNA.

For point (2), epinucleic heredity, it might still have been argued about whether there is any problem. Are there many examples, relevant to normal differentiation, where single cells transmit epigenetic information to a clone? (The skeptic had the advantage that the only somatic clone that occurs naturally is the zygote itself.) The ideal model for this process now is the heterochromatism of X-chromosomes in mammals (for which studies on human material have, once again, been consequential).

[2] *Science* 152:1463–1469, 1966.

As this phenomenon can be studied in cell culture, some crucial answers should soon be available on how the choice of heterochromatized chromosomes is initiated and perpetuated.

There is much more contention about tactics, and this may be the most glaring weakness. Epochs of revolutionary advance in biology have usually been connected with the convergence of many workers on some common, or reasonably comparable, experimental material: witness the role of *Drosophila* and maize for the growth of cytogenetics, and of *E. coli* B and its phages for the early delineation of the new virology. This convergence can, of course, be carried to a fault: Whatever else may have been brought up instead, we might have missed quite a bit but for the idiosyncrasy of E. L. Tatum and his students in working with another strain K-12, which was exhibitionistic enough to display sexuality, lysogenicity, and specialized transduction, all missing in the *E. coli* B/T-phage system. If any single experimental system in developmental biology had a fraction of the convergent attention that was given the T phages, we might be more optimistic about the pace of further work, but embryology suffers from being a traditional field, and seems to need the impulse of more novelty than frog gastrulae would now offer. Nor can we perceive who would or could play the disciplinary or rather disseminatory role that Max Delbruck did for phage. I have little doubt in my own mind that the mouse should be that central material, but this is a prejudice possibly based on expectations of utility from and for genetics, biochemistry, cytology, immunology, psychology, oncology, and medicine rather than on any significant personal experience. At the other pole, some very simple system like a rotifer or a nematode needs to be conventionalized—as much for the same array of ancillary fields as for embryology. Such conventions can hardly be imposed by any authority, but it might not be completely amiss for some group of investigators to attempt to find common ground by voluntary agreement, and to advertise the wisdom of their choice by their own good example.

My final remark as an outsider is that embryology is the branch of biology closest to human affairs, if only in the sense that man's intellect is the enduring morphogenesis of his brain. More broadly, the semilethal mutants that we count up only by the numbers in fruitflies are the congenital anomalies, mental retardation and recurrent stillbirth in man. A chemical factor that induces only a barely significant change in brain development in an experimental animal could have revolutionary consequences in a human context. The human life span is an almost

incidental side issue of his embryology. I would even put embryology ahead of genetics in the practical sphere, knowing that we can hardly be more than a generation away from the techniques for calculated manipulation of development that would take a millenium to match by any realizable program of artificial or natural selection. Finally, the genetic mechanism itself, like the determination of sex or the very need for a sexual process in reproduction, controls but is also an outcome of development.